REMARKS

I. Status Summary

Claims 1-45 are pending in the instant application.

Claims 1-45 have been subjected to a Restriction/Election Requirement. On January 18, 2005, Examiner Matthew C. Lee telephoned applicants' representative Richard E. Jenkins to discuss the Restriction Requirement. During the Telephone Interview, applicants' representative elected **Group I**, claims 1-16, 26-28, and 42, for prosecution. Applicants' representative further elected the following species for search:

1. species of crystallin protein (*e.g.* claim 8): gamma-crystallin
2. type of property (*e.g.* claim 13): antigen-binding specificity
3. species of vertebrate (*e.g.* claim 26): bovine (as amended).

Additionally, with regard to the Sequence Election Requirement, applicants' representative elected SEQ ID NO: 21 for search.

Applicants hereby confirm the election of Group I and the elected species. Applicants further note the decision by the United States Patent and Trademark Office (hereinafter "the Patent Office") to rejoin lipocalin with the elected species of protein to be mutagenized.

As a result of the election, claims 17-25, 29-41, and 43-45 have been withdrawn. Applicants reserved the right to file one or more divisional patent applications directed to the unelected subject matter. Claims 1-16, 26-28, and 42 are now pending in the subject U.S. patent application and have been examined.

All dependent claims have been objected to upon the assertion that the dependent claims should begin "The protein of claim..." instead of "Protein according to claim...".

Claims 1-16 and 26-28 have been rejected under 35 U.S.C. § 112, second paragraph, upon the contention that certain terms and phrases appearing in the claims are unclear. Particularly, the Patent Office contends that the phrase "wherein amino acids exposed on a surface of at least two β-strands exposed on a surface of

at least one beta sheet exposes on a surface of the protein" appearing in claim 1 is confusing. Additionally, the Patent Office contends that the phrase "wherein amino acids exposed on the surface of three beta strands exposed on the surface of the protein" appearing in claim 3 is also confusing.

Claims 1-6, 10, 11, 13, 16, 27, and 28 have been rejected under 35 U.S.C. § 102(a) upon the contention that the claims are anticipated by Beste *et al.* (96 PNAS 1898-1903, 1999; hereinafter "Beste").

Claims 1-13, 16, 26-28, and 42 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Chirgadze *et al.* (D52 Acta Cryst 712-721, 1996; hereinafter "Chirgadze") in view of Beste. Claims 1-6, 10, 11, 13-16, 27, and 28 have been rejected under this section upon the contention that the claims are unpatentable over Saviranta *et al.* (11 Protein Engineering 143-152, 1998; hereinafter "Saviranta") in view of Beste.

Claims 1-16, 26-28, and 42 have been amended. Support for the amendments can be found throughout the specification of the application as filed, including particularly at page 7, lines 23-25 (mutants having the desired binding properties and/or catalytic properties and/or fluorescence properties); at page 12, lines 7-9 (mutagenesis of beta-sheet proteins that do not have the recited properties such that, after mutagenizing amino acids in the beta-sheet, they acquire the recited properties), and at page 12, lines 32-34 (mutagenizing proteins that already have a recited activity or property prior to mutagenization and, after mutagenization in the beta-sheet, possess another, additional specific activity and/or property). Additional support for the amendments can be found in the claims as filed and in the Sequence Listing (bovine gamma-II-crystallin of SEQ ID NO: 22 and renumbering of amino acids in claim 12).

No new matter has been added by virtue of the claim amendments. Reconsideration of the application as amended and based on the remarks set forth below is respectfully requested.

II. Response to the Claim Objection

All dependent claims have been objected to upon the assertion that the dependent claims should begin "The protein of claim..." instead of "Protein according to claim...". Applicants respectfully traverse the objection as applying a requirement for claim form and terminology that is not mandatory. Applicants respectfully submit that there is no formal requirement that dependent claims begin with "The [composition/process/etc.] of claim X". Thus, applicants respectfully submit that the Patent Office has applied an improper standard in presenting the instant objection.

However, in an effort to facilitate prosecution of the pending claims, applicants have amended claims 2-16 and 26-28 (*i.e.*, all pending dependent claims) as required by the Patent Office. Applicants respectfully submit that the amendments to the claims are solely to comply with the form required by the Patent Office, and are not to be construed as a surrender of any subject matter encompassed by the claims prior to the amendments.

Applicants respectfully submit that the amendments to claims 2-16 and 26-28 address the instant objection, and respectfully request that the objection be withdrawn at this time. Accordingly, applicants respectfully submit that claims 2-16 and 26-28 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

III. Responses to the Rejections under § 112, Second Paragraph

Claims 1-16 and 26-28 have been rejected under 35 U.S.C. § 112, second paragraph, upon the contention that certain terms and phrases appearing in the claims are unclear. Particularly, the Patent Office contends that the phrase "wherein amino acids exposed on a surface of at least two β-strands exposed on a surface of at least one beta sheet exposes on a surface of the protein" appearing in claim 1 as confusing. Additionally, the Patent Office contends that to the phrase "wherein amino acids exposed on the surface of three beta strands exposed on the surface of the protein" appearing in claim 3 is also confusing.

After careful consideration of the rejections and the Patent Office's basis therefor, applicants respectfully traverse the rejections and submit the following remarks.

According to the Patent Office, the repeated use of the term "exposed" in the phrase "wherein amino acids exposed on a surface of at least two β-strands exposed on a surface of at least one beta sheet exposes on a surface of the protein" confuses the relationship among the objects referred to in the claim, and as a result, it is not clear how the amino acids are related to the surface and beta sheet of the protein. Applicants respectfully submit, however, that the phrase at issue clearly defines the metes and bounds of the claim when considered from the perspective of the skilled artisan in light of the specification.

Applicants respectfully submit that beta-sheets are structural elements of proteins that are themselves formed of several beta-strands. Beta-sheets can either be buried in the interior part of the protein or located on its surface. In addition, an arrangement representing a mixture of both possibilities can often be found within proteins. In the latter case, some beta-strands (forming a beta-sheet structure) can be found in the interior part of the protein while other beta-strands are exposed on the surface of the protein (*i.e.*, located on the surface of the protein).

The terms "surface" and "exposed" were used in the claim to particularly point out and distinctly recite the presently disclosed subject matter. In accordance with the presently disclosed subject matter, amino acids of the starting protein are mutagenized that are located on the surface of the protein. This is *inter alia* described on page 2, last paragraph, on page 7, second paragraph, as well as on page 8, first paragraph to page 9, second paragraph, of the specification. The amino acids selected to be mutagenized must themselves be located within at least two beta-strands. The beta-strands themselves form a beta-sheet, and the two beta-strands including the mutagenized amino acids are located within at least one beta-sheet. Applicants respectfully submit that the phrases at issue clearly describe this approach.

Applicants further respectfully submit that § 2173.02 of the Manual of Patent Examining Procedure (hereinafter "the MPEP"),

> The examiner's focus during examination of claims for compliance with the requirement for definiteness of 35 U.S.C. 112, second paragraph, is whether the claim meets the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available.

Applicants respectfully submit that the language at issue in claim 1 provides sufficient clarity and precision. The language and modes of expression chosen adequately convey the metes and bounds of claim 1, and thus applicants respectfully submit that the instant rejection is improper. Similarly with regard to claim 3, applicants respectfully submit that the phrase "wherein amino acids exposed on the surface of three beta strands exposed on the surface of the protein" similarly conveys the metes and bounds of claim 3. Thus, applicants respectfully submit that the metes and bounds of claim 3 are also clearly recited.

Nonetheless, in an effort to facilitate prosecution of the pending claims, applicants have amended claim 1 to recite *inter alia* a protein with beta-sheet structure, wherein amino acids on a surface of the protein located within at least two β-strands of at least one beta sheet are mutagenized. Claim 3 has been amended to recite the protein of Claim 1, wherein amino acids located within three beta strands exposed on the surface of the protein are mutagenized. Support for these amendments can be found throughout the specification as filed, including particularly at page 8, lines 22-24; page 9, lines 9-11; and in original claims 1 and 3.

Applicants respectfully submit that the amendments to claims 1 and 3 address the instant rejections under 35 U.S.C. § 112, second paragraph, and respectfully request that the rejections be withdrawn at this time. Applicants further respectfully submit that claims 1-16 and 26-28 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

IV. Response to the Rejection under § 102

Claims 1-6, 10, 11, 13, 16, 27, and 28 have been rejected under 35 U.S.C. § 102(a) upon the contention that the claims are anticipated by Beste. According to the Patent Office, Beste discloses an engineered protein derived from a beta sheet structured protein (lipocalin) with a new antigen binding specificity. Beste is further asserted to teach a set of criteria for selecting amino acids to be mutagenized, and to anticipate the various possible combinations of amino acids to be mutagenized as recited in claims 3-6, 10, 11, 13, 27, and 28. Finally, the Patent Office asserts that the composition of claim 16 is anticipated by the solution of the ELISA binding assay as taught by Beste.

After careful consideration of the rejections and the Patent Office's basis therefor, applicants respectfully traverse the rejections and submit the following remarks.

Applicants respectfully direct the Patent Office's attention to amended claim 1, which recites the following:

> A protein with beta-sheet structure, wherein amino acids on a surface of the protein located within at least two β-strands that form at least one beta sheet are mutagenized, wherein the mutagenizing is selected from the group consisting of an insertion, a deletion, a substitution, and combinations thereof, such that the protein has a new property selected from the group consisting of an antigen binding specificity, a catalytic activity, a fluorescence property, and combinations thereof, with the proviso that:
>
> (i) the protein without substitution, deletion, or insertion has no binding activity, catalytic activity, or fluorescence property at the surface of the beta-sheet structure wherein the amino acids are mutagenized, and after substitution, deletion, or insertion at the surface of the beta-sheet structure, the protein has the new property selected from the group consisting of an antigen binding specificity, a catalytic activity, a fluorescence property, and combinations thereof; or
>
> (ii) the protein has a binding activity, catalytic activity, or fluorescence property before the substitution, deletion, or insertion, and that after the substitution, deletion, or insertion at the surface of the beta-sheet structure, the

> protein has an additional new binding activity, an additional new catalytic activity, an additional new fluorescence property, or combinations thereof.

Support for the amendment can be found in the specification as filed at page 12, line 27, through page 13, line 2.

Applicants respectfully submit that Beste teaches an engineered protein derived from a beta-sheet structured lipocalin, wherein the *already existing* antigen-binding specificity was altered in order to create a different ligand specificity. Applicants respectfully submit that the approach recited in claim 1 is quite different. First of all, applicants respectfully submit that Beste do not describe the creation of a synthetic binding site *de novo* on the surface of a protein. The lipocalin of Beste is a bilin-binding protein (BBP) and has, therefore, an already existing ligand-binding pocket. It is this already existing ligand-binding pocket that is mutagenized in Beste, and thus the mutagenized protein of Beste falls outside of element (i) of the proviso recited in claim 1.

Secondly, Beste does not disclose element (ii) of the proviso recited in claim 1. To elaborate, page 1900, right column, first full paragraph of Beste discloses the criteria for selecting the amino acid positions to be mutagenized. These two criteria are that (a) the residues should make contact to the natural ligand of BBP, and (b) they should in principle tolerate both small and large side-chain substitutions. These criteria clearly imply that the amino acid positions chosen are located at the center of the lipocalin's ligand-binding, which is confirmed in the first sentence of the cited passage.

On the contrary, the present subject matter, as recited in claim 1, excludes the use of naturally occurring binding sites for creating new binding specificities. Instead, element (ii) of the proviso clearly recites that if the non-mutagenized protein has a binding, catalytic, or fluorescence activity, the mutagenesis creates an additional binding specificity, catalytic activity, and/or fluorescence property. The term "additional" indicates that the prior existing binding specificity or catalytic activity or

fluorescence property is maintained while a further new additional property is created *de novo* at a site different from the pre-existing binding pocket. This aspect of the presently claimed subject matter is disclosed in the specification as filed on page 12, line 27, through page 13, line 2.

Applicants respectfully submit that this is contrary to the teaching of Beste, which discloses the mutagenesis of amino acids at the center of an already existing ligand-binding pocket to alter an already existing binding activity. Thus, applicants respectfully submit that neither element (i) nor element (ii) is disclosed in Beste, and thus applicants respectfully submit that Beste does not support the instant rejection of claim 1.

Applicants respectfully submit that one example of the presently disclosed subject matter is the family of crystallin proteins, which are structural proteins having no specific binding properties. Crystallins are recited in claims 2, 7-9, 12, 26, and 42. Using a crystallin (*e.g.*, a bovine gamma-II-crystallin) as a starting protein, mutagenization of amino acids located within at least two beta-strands that form at least one beta sheet located on a surface of the protein yields a crystallin protein with a binding specificity comparable to an antibody using a starting material that has no specific binding activity. The non-mutated lipocalins employed by Beste, on the other hand, already are characterized by a binding activity, and the modifications suggested by Beste refer to amino acids within the binding pocket of the lipocalins that are spread across four loop regions and not to the regions which are not involved in the binding pocket.

Accordingly, applicants respectfully submit that the rejection of claim 1 under 35 U.S.C. § 102(a) upon the contention that the claims are anticipated by Beste has been addressed. Applicants further respectfully submit that claims 2-6, 10, 11, 13, 16, 27, and 28 all depend directly or indirectly from claim 1, and thus also are believed to be patentably distinguished from Beste based on their dependence from distinguished claim 1. Thus, applicants respectfully request that the instant rejection be withdrawn at this time. Applicants further respectfully submit that claims 1-6, 10,

11, 13, 16, 27, and 28 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

V. *Responses to the Rejections under § 103*

Claims 1-13, 16, 26-28, and 42 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Chirgadze in view of Beste. Claims 1-6, 10, 11, 13-16, 27, and 28 have been rejected under this section upon the contention that the claims are unpatentable over Saviranta in view of Beste.

After careful consideration of the rejections and the Patent Office's basis therefor, applicants respectfully traverse the rejections and submit the following remarks.

V.A. *Response to the Rejection over* Chirgadze *in view of* Beste

According to the Patent Office, Chirgadze teaches a crystal structure of bovine gamma-II-crystallin, which is asserted to have a Greek-key beta-sheet motif with amino acids exposed on the surface. Chirgadze is also asserted to teach that the mutation of H15C affects surface hydrophobicity/hydrophilicity and there are surface exposed clusters of residues including Lys2, Glu17, Arg36, and Asp38.

The Patent Office concedes, however, that Chirgadze does not teach mutagenizing the surface exposed residues to arrive at a new antigen-binding activity. This deficiency is asserted to be cured by Beste, which the Patent Office contends teaches mutagenizing selected amino acids residues of lipocalin to produce a new antigen-binding activity and the general criteria for selecting amino acids to mutagenize. The Patent Office thus asserts that it would have been obvious to one of ordinary skill in the art at the time of the invention to mutagenize any of Lys2, Glu17, Arg36, and Asp38, forming a highly charged cluster of surface residues on the beta-sheet structure of bovine gamma-II-crystallin as taught by Chirgadze using the engineering principle and criteria as taught by Beste, where the motivation would

have been to apply the design principles to the crystallin structure of Chirgadze as an alternate protein scaffold for the design of novel binding site.

Initially, applicants wish to point out that Chirgadze does not teach the crystal structure of a bovine gamma-II-crystallin, but instead teaches the crystal structure of a bovine gamma-IIIb-crystallin.

Furthermore, applicants respectfully submit that the Patent Office has not presented a *prima facie* case of obviousness of claims 1-13, 16, 26-28, and 42 because the Patent Office has not pointed out any motivation to combine the references that does not depend on hindsight. The Patent Office asserts that "the motivation would have been to apply the design principles to the crystallin structure of Chirgadze as an alternate protein scaffold for the design of novel binding site". Official Action at page 10 (citing Beste at page 1903, left column, 3rd paragraph).

The Patent Office fails to demonstrate, however, that upon a reading of Beste, one of ordinary skill in the art would have considered gamma crystallins to be good candidates for the design of novel binding sites. In fact, as discussed in more detail hereinbelow, applicants respectfully submit that when the teaching of Beste is viewed in its entirety, one of ordinary skill in the art would not have looked to crystallins as scaffold candidates because the method of operation of the Beste method would be inapplicable to crystallins. Thus, applicants respectfully submit that one of ordinary skill in the art would have had no motivation to combine Beste with Chirgadze.

Applicants respectfully direct the Patent Office's attention to the discussion hereinabove regarding the teachings of Beste, which are appropriately viewed as being directed to the alteration of a pre-existing ligand-binding domain to acquire an altered binding specificity. Applicants respectfully submit that the Patent Office's assertion that Beste teaches a general method of engineering a beta-sheet protein by mutagenizing selected amino acid residues resulting in a new antigen-binding specificity can only derive from a hindsight reconstruction of the reference in view of the instant specification. As a result, applicants respectfully submit that the combination of Beste and Chirgadze does not support the instant rejection.

Unlike the teachings of the cited combination of Chirgadze and Beste, the presently disclosed subject matter is not directed to modification of a pre-existing binding domain, but instead relates to the creation of a new domain in a protein that either endows a protein that does not have binding, catalytic, or fluorescent activities with a *de novo* binding activity, catalytic activity, and/or fluorescence property, or alternatively endows a protein that does have binding, catalytic, or fluorescent activities with an additional binding activity, catalytic activity, and/or fluorescence property. Applicants respectfully submit that the proposed combination of the Beste and Chirgadze references does not disclose or suggest mutagenizing a protein that does not have binding, catalytic, or fluorescence activity in order to produce a mutagenized protein that does have one or more of these activities as recited in claim 1 under proviso (i). Additionally, applicants respectfully submit that the proposed combination of the Beste and Chirgadze references does not disclose or suggest mutagenizing a protein that does have a binding, catalytic, or fluorescence activity in order to produce a mutagenized protein that has an additional one or more of these activities as recited in claim 1 under proviso (ii).

Applicants respectfully submit that at best Beste might suggest modifying an existing ligand-binding pocket to create an altered ligand-binding specificity. However, given that the crystallin of Chirgadze does not have a ligand-binding pocket, applicants respectfully submit that one of ordinary skill in the art would have had no motivation to combine the two cited references as suggested by the Patent Office because the modification strategy of Beste when properly construed cannot be applied to a crystallin.

Stated another way, the Patent Office acknowledges that Chirgadze does not teach replacing any amino acids on the surface of crystallins to arrive at a new antigen-binding activity. The Patent Office asserts, however, that this deficiency is cured by Beste, which is asserted to teach engineering a beta-sheet protein by mutagenizing selected amino acid residues to result in a new antigen-binding activity, and which is further asserted to teach the general criteria for selecting the amino

acids to mutagenize. As crystallins do not have pre-existing binding pockets, the presence of which is a requirement according to Beste (*see* page 1900, right column, first full paragraph), applicants respectfully submit that there would be no motivation for a skilled artisan to employ crystallins instead of lipocalins.

Additionally, applicants respectfully submit that by comparing the amino acid sequences of gamma-crystallin D and B, Chirgadze found three amino acid residues that differ between these crystallin species. These main determinants of the different intermolecular interactions during crystal packing of the two gamma-crystallin species gammaB and gammaD are ascribed to residues Leu51, Ile103 and His155 (page 719, chapter 3.5, 4th sentence). Apart from the fact that crystal packing interactions can be highly artificial, these residues are far away from, for example, those residues suitable for the generation of a *de novo* binding site. Indeed, applicants respectfully submit that these residues are not located within a beta-strand on the surface of the protein.

Furthermore, Chirgadze teach that charged cluster residues are very conserved among different vertebrate crystallins (*see* page 718, last paragraph). Applicants respectfully submit that these residues would not be suitable for random mutagenesis according to Beste. Highly conserved residues do not fulfill the pre-requisite for randomization given by Beste at page 1900, right column, first paragraph, to exhibit tolerance towards both small and large side chain substitutions. This high degree of conservation would be expected to have important implications for the structural integrity of the crystallins, and modifications to other amino acids (such as those with either small or large side chains) would be expected to interfere with, if not destroy, the structural integrity of the molecule. For this reason, applicants respectfully submit that the structural conservation taught in Chirgadze teaches against the use of crystallins in the method of Beste.

Accordingly, applicants respectfully submit that the Patent Office has not presented a *prima facie* case of obviousness of independent claims 1 and 42 over Chirgadze in view of Beste. Claims 2-16 and 26-28 all depend directly or indirectly

from claim 1, and are thus also believed to be distinguished from the cited combination. Thus, applicants respectfully request that the instant rejection be withdrawn at this time. Applicants further respectfully submit that claims 1-16, 26-28, and 42 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

V.B. Response to the Rejection over Saviranta *in view of* Beste

Claims 1-6, 10, 11, 13-16, 27, and 28 have been rejected under this section upon the contention that the claims are unpatentable over Saviranta in view of Beste. According to the Patent Office, Saviranta teach engineering using random mutagenesis of an antibody to gain binding specificity towards estradiol and other derivatives. The Patent Office concedes, however, that Saviranta does not teach engineering a beta-sheet structured protein to have binding specificity toward estradiol.

This deficiency is asserted to be cured by Beste. According to the Patent Office, it would have been obvious to one of ordinary skill in the art to apply the beta-sheet structured protein engineering protocol taught by Beste to redesign a beta-sheet structured protein to bind to estradiol, similar to the protein engineering of antibody taught by Saviranta, wherein the motivation would have been to replace the bulkier antibody molecule with smaller beta-sheet structured protein scaffolds as taught by Beste. This rejection is respectfully traversed.

The Patent Office has characterized the teachings of Saviranta as "engineering using random mutagenesis of an antibody to gain binding specificity towards estradiol and other derivatives". Official Action at page 10. However, applicants respectfully submit that this is a selective reading of the reference that does not take into account what the reference fairly suggests to the skilled artisan when the disclosure is viewed in its entirety. As the Court of Customs and Patent Appeals stated in In re Wesslau, "[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a

given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art" (353 F.2d 238, 241, C.C.P.A. 1965).

Applicants respectfully submit that Saviranta teaches the engineering of an antibody fragment using random mutagenesis. However, the Fab molecule of Saviranta is derived from a classical monoclonal antibody obtained by immunization of mice with estradiol. Consequently, the molecule engineered by Saviranta already possesses an ability to bind the hapten estradiol, and thus Saviranta teaches a molecule that binds estradiol before any mutagenesis is performed.

Furthermore, applicants respectfully submit that careful review of Saviranta demonstrates that the strategy employed was not to create a new or additional binding specificity as recited in claim 1 of the instant application, but rather was designed to destroy the ability of the already available anti-estradiol antibodies to cross react with testosterone. Thus, applicants respectfully submit that at best Saviranta suggests that the binding of an antibody to an antigen can be fine-tuned to eliminate cross reactivity with related molecules. In fact, Saviranta clearly indicates that even after mutagenesis "estradiol affinities were mainly unchanged". *See e.g.*, Saviranta, Abstract.

Thus, applicants respectfully submit that Saviranta does not teach using an antibody as a scaffold to create a new or additional binding specificity as recited in claim 1. Applicants respectfully submit that the approach disclosed in Saviranta is similar to that of Beste, in which a pre-existing ligand-binding site is engineered to produce an altered binding specificity. As a result, applicants respectfully submit that the cited combination of Beste and Saviranta at best teaches that pre-existing ligand-binding domains of proteins can be mutagenized to alter the specificity of the ligand-binding domain. As a result, applicants respectfully submit that even if Saviranta and Beste were combined as asserted by the Patent Office, the combination would not and indeed, does not each and every element of claim 1.

To elaborate, claim 1 recites *inter alia* selective mutagenesis of a protein with beta-sheet structure, wherein amino acids on a surface of the protein located within at least two β-strands of at least one beta sheet are mutagenized to create new or additional antigen-binding activities, catalytic activities, and/or fluorescence properties *de novo* in the beta-sheet structures of the protein. Applicants respectfully submit, therefore, that the subject matter of the instant claims involves mutagenizing amino acids located within non-flexible, rigid regions of a protein, more particularly, beta-strands in a beta-sheet, and modifying these regions of a protein in order to create a new or additional binding activity, fluorescence property, catalytic activity, and combinations thereof. Applicants respectfully submit that this is not taught or suggested by the cited combination of Saviranta and Beste.

Thus, applicants respectfully submit that when taken in context and in their entireties, the Saviranta and Beste references do not support a rejection of claim 1 under § 103 because the combination does not teach or suggest that regions of a beta sheet protein not normally associated with ligand binding can be mutagenized in order to gain new or additional ligand-binding specificities at sites other than pre-existing ligand-binding domains.

Accordingly, applicants respectfully submit that the combination of Saviranta and Beste do not support a *prima facie* case of obviousness of claim 1. Claims 2-6, 10, 11, 13-16, 27, and 28 all depend directly or indirectly from claim 1, and thus are also believed to be distinguished from the combination of Saviranta and Beste. Applicants respectfully request that the instant rejection be withdrawn at this time. Applicants further respectfully submit that claims 1-6, 10, 11, 13-16, 27, and 28 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

CONCLUSIONS

Should there be any minor issues outstanding in this matter, the Examiner is respectfully requested to telephone the undersigned attorney. Early passage of the subject application to issue is earnestly solicited.

Application Serial No.: 10/030,605

Deposit Account

The Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account Number **50-0426**.

Respectfully submitted,

JENKINS, WILSON & TAYLOR, P.A.

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